



Research Article

EFFECTS OF POLICOSANOL IN OLDER PATIENTS CONSUMING NITRATES VASODILATORS

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ABSTRACT

Background: Policosanol is a cholesterol-lowering drug with concomitant antiplatelet effects. The efficacy and safety of policosanol have been investigated in clinical studies and post-marketing surveillance. Policosanol is very safe and no drug-related adverse events have been demonstrated, even in population subsets with high consumption of concomitant therapy, indicating that the potential risk of drug-drug interaction for policosanol is low. Vasodilators are used in geriatric populations mainly to treat congestive heart failure and acute decompensating of heart failure, although associated to other anti-hypertensive are also used for manage hypertension. Vasodilators, however, have considerable risk of drug-related toxicity, the most frequent symptoms being those derived from excessive vasodilation and hypotension, such as nausea, vomiting, loss of consciousness and reflex tachycardia. Vasodilators show important drug-drug interaction derived from pharmacodynamic interactions with several drugs, those associated to concomitant use of other vasodilators and diuretics being the most relevant. Considering such facts, the interest to study putative drug-drug interaction between policosanol and vasodilators is supported. Objective: To investigate whether policosanol administered to older patients consuming vasodilators induces any specific disturbance on safety indicators and/or increase the frequency or severity of adverse events in such patients. Methods: This report was based in the analysis of the records of all patients (185) taking nitrates vasodilators included in a Prevention Study in the Elderly randomised to policosanol 5 mg/d or placebo for 3 years. Analysis was by Intention-to-treat. Results: Baseline characteristics were well balanced in both groups. After one year on treatment, policosanol lowered significantly low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC) and triglycerides (TG), whereas raised high-density lipoprotein-cholesterol (HDL-C). Policosanol effects persisted, even increased, during the 3 years treatment. At the end of the study, policosanol reduced LDL-C (35%), TC (25%), TG (19,3%) and raised HDL-C (16,7%). Of 185 randomised patients taking vasodilators, 44 (23,8 %) withdrew from the trial. The frequency of withdrawals in placebo (31/95; 32,6 %) was greater ($p < 0,01$) than in policosanol group (13/90; 14,4 %). Overall, 26/185 (14,1 %) patients discontinued due to some adverse events: 23 placebo (24,2 %) and 3 (3,3 %) policosanol patients ($p < 0,01$). Policosanol did not impair safety indicators compared with placebo, but induced additional decreases of systolic pressure compared with placebo, but no individual value or clinical symptom of hypotension was reported. The frequency of policosanol patients experiencing serious adverse events (3/90; 3,3 %) was lower ($p < 0,01$) than in respective placebo (23/95; 24,2 %). Likewise, the frequency of policosanol patients who experienced some mild or moderate adverse events during the study (10/90; 11,1 %) was lower ($p < 0,05$) than in matched placebo (28/95; 29,5 %). Conclusions: These results indicate that policosanol can be administered to older patients taking vasodilators without risk of relevant adverse drug-drug interaction.

Keywords: policosanol, elderly, cholesterol-lowering, anti-hypertensive, vasodilators, adverse events

INTRODUCTION

Atherosclerotic disease is a major cause of morbidity and mortality in middle-aged and older adults.¹ In particular, coronary heart disease (CHD) is the leading cause of death in adult population worldwide, coronary events being directly related to raised serum levels of low-density lipoprotein cholesterol (LDL-C).² End-point clinical trials have convincingly demonstrated the benefits of lowering LDL-C with statins on coronary events.³⁻⁷ Thus, hypercholesterolemia management in adults is a cornerstone of coronary prevention guidelines.⁸

Nevertheless, the treatment of hypercholesterolemia in the elderly was strongly controversial due to elevated LDL-C levels decrease as predictors of relative coronary risk with age.⁹ Older individuals are particularly prone to drug-related adverse events (AE), due to they have impaired hepatic and renal drug clearance, electrolyte imbalance, several concomitant diseases and concomitant therapies.⁹ In particular, the risk for drug-drug interactions (DDI) in this population is increased respect to younger adults.⁸ Considering that elevated LDL-C values still are strong predictors of absolute coronary risk in the elderly,⁹ and the results of strata

analysis performed in subgroups of older patients included in end-point studies that demonstrated the benefits of lowering LDL-C in these cases,³⁻⁷ treatment of hypercholesterolemia in the elderly is now recommended.⁹

Policosanol is a mixture of high molecular weight alcohols isolated from sugar cane wax¹⁰ with cholesterol-lowering effects demonstrated in type II hypercholesterolemia¹¹⁻²¹ and the dyslipidemia due to Type 2 diabetes mellitus,²⁴⁻²⁶ including older individuals. Policosanol (5-20 mg/d) decreases LDL-C and TC levels, increases high-density lipoprotein cholesterol (HDL-C) and induce modest and not reproducible effects on triglycerides (TG).¹⁰⁻²⁴

Policosanol inhibits cholesterol biosynthesis between acetate consumption and mevalonate production²⁵⁻²⁷ by suppressing HMG-CoA reductase up-regulation, through a depression of the synthesis of the enzyme and/or stimulation of its degradation.²⁷ Policosanol increases LDL receptor-dependent processing,²⁵ enhancing the catabolic rate of such lipoprotein.²⁶ Policosanol also inhibits platelet aggregation^{10,16,28} and LDL lipid peroxidation.^{29,30}

Clinical and post-marketing surveillance studies have demonstrated that policosanol is very safe and well tolerated,^{10-24,31,32} even in populations with high consumption of concomitant drugs. The frequency of adverse events (AE) in policosanol patients has been similar or even lower than in placebo, no drug-related AE being proven up to date. Hence, adverse drug-drug interactions (DDI) with policosanol appear to be not relevant.

DDI are based in pharmacokinetic and/or pharmacodynamic interactions. Experimental data indicate that DDI between policosanol and drugs metabolised through the cytochrome P450 hepatic system are not expected, and did not modify the activity of hepatic drug-metabolising enzymes.³³ Since most drugs are metabolised by this system, the risk for DDI based in pharmacokinetic interactions with policosanol is low.

Nevertheless, pharmacodynamic DDI with policosanol could be possible. Thus, different clinical studies have shown that policosanol can induce reductions of both systolic and/or diastolic pressure compared with placebo. Thus, potential DDI with drug lowering blood pressure need to be investigated.

Vasodilators are used in geriatric populations mainly to treat congestive heart failure and acute decompensating of heart failure, although associated to other anti-hypertensive are also used for manage arterial hypertension.³⁴

Vasodilators, however, have considerable risk of drug-related toxicity, the most frequent symptoms being those derived from excessive vasodilation and hypotension, such as nausea, vomiting, loss of consciousness and reflex tachycardia. Although less frequent, after prolonged use, vasodilators can induce serious toxicity coming from accumulation of thiocyanate, thus resembling cyanide-poisoning symptoms, such as toxic pink mucosae, psychosis and metabolic acidosis. Vasodilators show important DDI derived from pharmacodynamic interactions with several drugs, those associated to concomitant use of other vasodilators and diuretics being the most relevant.^{34,35} Then, the rationale for investigating DDI between policosanol and vasodilators, especially in the elderly, is supported. The present analysis was performed to determine whether policosanol administered concomitantly with vasodilators to older patients impairs any safety indicator and/or induce some specific AE. Likewise, we investigated if cholesterol-lowering efficacy of policosanol in these patients is that expected.

PATIENTS AND METHODS

The present analysis includes the data of all patients consuming vasodilators included in the Prevention Study of policosanol in the elderly.³⁶

Ethics considerations: An independent Ethics Committee approved study protocol before study starting. All patients were enrolled after providing informed written consent.

Study Design: Patients were enrolled at four Policlinical Centres: "Ramón González Coro"; "Elpidio Berovides," "Educational" and "26 de Julio" from the Havana city zones named Marianao, Lisa and Playa, being followed by medical staff of the Surgical Medical Research Centre. The personnel involved in patient treatment were blinded to treatment allocation.

Enrolled patients (visit 1) were instructed to follow a step one cholesterol-lowering diet for 5 weeks of a diet-only baseline period. After that, lipid profile and safety laboratory indicators were assessed, and the following week patients attended to visit 2. The laboratory values obtained after the baseline period and safety physical indicators determined at visit 2 were baseline values. Eligible patients were randomized, under double-blind conditions, to policosanol 5 mg or placebo tablets. Concomitant

medications taken by study patients were recorded. The patients were followed every 3 months during the first year (visits 3 to 6) and every 6 months thereafter (visits 7-10).

Enrolled criteria: Women and men aged 60-80 with documented CHD, cerebrovascular disease, hypertension, dyslipidemia, smoking habits or/and diabetes. The rationale for the lowest cut-off for age was to include older subjects with enough life expectancy.

Inclusion criteria: Patients were randomized if showed serum TC ≥ 5.2 , LDL-C ≥ 3.4 and TG < 4.52 mmol/L after the diet-only baseline period.

Exclusion criteria: Patients were excluded if had active renal or diagnosed neoplastic diseases, severe hypertension (diastolic pressure ≥ 120 mm Hg), uncontrolled diabetes or poor cognitive function. Patients with history of unstable angina, myocardial infarction, stroke or any serious AE (SAE) within the 3 months prior to recruitment were also excluded.

Withdrawal criteria: Any AE justifying such decision, unwillingness to continue, TC ≥ 9 mmol/L or major violations of study protocol (including > 6 weeks without taking the study drugs).

Treatment: Appearance and packages of study drugs were identical, packages identified by a code number assigned at each Policlinic by progressive inclusion. Treatment was randomised through a random allocation of balanced block of size ten, with a randomization ratio 1:1. Tablets were taken once a day (oid) with evening meal. Participants in both groups should be titrated to 2 or 4 tablets oid if TC levels were ≥ 7 mmol/L after 6 or 12 months on therapy.

Compliance assessment: Compliance with study medications was assessed from visits 3 to 10 by tablet counts and patient request.

Concomitant medications: Consumption of lipid-lowering drugs was prohibited from the enrolment in the study, but no other restriction for concomitant therapy was done. Cases at secondary prevention were advised to take daily aspirin. Concomitant drugs were controlled through patient questioning, with additional interview to Family Doctors, if necessary.

Assessments: TC was assessed at baseline and every 6 months. Lipid profile and safety laboratory tests were determined at baseline and 1, 2 and 3 years thereafter. Laboratory tests included lipid profile, glucose, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

At each visit physical examination and dietary guiding were done. Compliance assessment and request for AE were performed from visits 3 to 10. Compliance was defined as good if ≥ 85 % of the scheduled tablets having been consumed since the prior visit.

Effects on lipid profile: Changes on LDL-C were the primary efficacy variable to assess the cholesterol-lowering efficacy of policosanol, treatment being considered as effective if LDL-C was significantly reduced by ≥ 15 % respect to baseline.³⁷ Changes on other lipid profile parameters were also analysed.

Safety and tolerability analyses: Patient records were reviewed. Data from all patients taking vasodilators were included in the analysis. Physical indicators (body weight, pulse rate, blood pressure) and laboratory values (glucose, creatinine, AST, ALT)

were analysed. Safety and tolerability analysis included data on SAE, moderate and mild AE.

An AE was defined as any new undesirable event or change in physical or laboratory data or the worsening of any pre-existing condition happened through the study.

AE were classified according to their intensity in mild, moderate and serious. Mild AE not required the treatment of AE or withdrawal of study drugs, moderate AE required withdrawal of study medication and/or treatment of the AE. A SAE was considered any AE leading to patient hospitalisation or death.

The End-point Committee of the whole study blindly reviewed and categorized endpoint data, the events being diagnosed and classified by personnel blinded to treatment allocation and not involved in the trial. For each category, events with definite + suspect causes were included. In the whole study, events were analysed according by time of first event. In the present analysis, the sample size and event number was too small for survival and hazard ratio analyses, the groups being compared by relative proportions.

Laboratory analysis: Blood samples were drawn after a 12 hours overnight fasting. Serum TC, LDL-C, HDL-C and TG were determined by enzymatic methods using reagent kits. Laboratory analyses were performed in the Hitachi 719 autoanalyzer (Tokyo, Japan) located at the Medical Surgical Research Centre. A quality control of the precision and accuracy of the methods was performed.

Statistical analysis: Statistical analysis followed the plan specified in study protocol or in amendments. All data were analyzed according to Intention to-treat principle.

ANOVA test was used to compare continuous variables throughout the study. Comparisons between groups of categorical data were made by Fisher's Exact Probability test. All statistical tests were two-tailed, with significance at $\alpha=0,05$. Statistical analyses were performed using Statistic for Windows (Release 4.2; Copyright StatSoft, Inc. US) and SAS/STAT (Stat Soft, Version 8, US).

RESULTS

Baseline patient characteristics: Both groups were well-balanced respect to main baseline characteristics (Table 1). Most patients were women (155/185; 83,8 %) average age at randomisation being 68 years old. The frequency of study patients with CHD (166/185; 89,7 %) and hypertension (147/185; 79,5 %) was very high, the frequency of diabetes being also relatively high (41/185; 22,2 %).

The vasodilator most consumed by study patients was nitropental, followed by isosorbide nitrate and nitroglycerin. The frequency of other concomitant therapies among study patients was high, those more frequently taken being anti-platelets, calcium antagonists, diuretics, β -blockers, diuretics, oral hypoglycemic drugs and digitalics, among others. Both groups were well-balanced respect to other concomitant drugs too.

Withdrawal analysis: Table 2 shows withdrawals analysis. As observed, the total number of withdrawals was significantly lower

in policosanol than in placebo. Of 185 randomised patients taking vasodilators, 44 (23,8 %) withdrew from the trial.

The frequency of withdrawals in placebo (31/95; 32,6 %) was greater ($p < 0,01$) than in policosanol group (13/90; 14,4 %). Overall, 26/185 (14,1 %) patients discontinued due to some AE: 23 placebo (24,2 %) and 3 (3,3 %) policosanol patients ($p < 0,01$).

Compliance: Compliance with study medications was good according to compliance criterion.

Effects in serum lipid profile: Table 3 shows the effects on lipid profile. Both groups were well matched regarding all lipid profile variables at randomisation.

After one year on treatment, policosanol lowered significantly ($p < 0,0001$ vs placebo) LDL-C (20,9 %), TC (15,9 %) and TG (19,3 %), whereas raised HDL-C (8,3 %).

Policosanol effects persisted, even increased, during the 3 years treatment. At the end of the study, policosanol reduced ($p < 0,0001$ vs baseline and placebo) LDL-C (35,0 %), TC (25,0 %), TG (19,3 %) and raised ($p < 0,0001$ vs placebo) HDL-C (16,7 %).

Safety and tolerability: Policosanol did not impair safety indicators compared with placebo (Table 4), but after one year on therapy induced additional decreases of systolic pressure compared with placebo, that were maintained up to study completion. A mild, but significant reduction of systolic pressure was also observed at the end of the study compared with placebo. Nevertheless, no individual value or clinical symptom of hypotension was reported. Values of both serum transaminases (ALAT and ASAT) were also lower in policosanol than in placebo group from one year after treatment up to the final check-up.

Twenty-six (26) (14,1 %) withdrawals were due to some AE: 23 in placebo (24,2 %) and 3 (3,3 %) in policosanol group ($p < 0,01$). Table 5 summarizes the frequency of SAE occurred during the study. The frequency of policosanol patients experiencing SAE (3/90; 3,3 %) was significantly lower ($p < 0,01$) than in respective placebo (22/95; 23,2 %). Seven patients (6 placebo, 1 policosanol) died during the study. All placebo died due to vascular events, while the policosanol patient died due to adenocarcinoma de colon.

Table 6 summarizes all moderate and mild AE reported during the study. As can be observed, no AE was particularly increased in policosanol group respect to placebo. Overall, the frequency of policosanol patients who experienced some mild or moderate AE during the study (10/90; 11,1 %) was lower ($p < 0,05$) than in matched placebo (28/95; 29,5 %).

DISCUSSION

The present report demonstrates that in older hypercholesterolemic patients receiving vasodilators, policosanol induced persistent reductions of LDL-C and TC, while increased HDL-C, without impairing any safety indicator or increasing the frequency of AE. By the contrary, the frequency of SAE and all AE was lower in policosanol than in placebo.

Table 1: Main baseline characteristics of study patients

| Characteristics | Placebo (n = 95) | | Policosanol (n = 90) | |
|--|------------------|------|----------------------|------|
| Age (years) (X±SD) | 68 ± 6 | | 68 ± 6 | |
| Body mass index (kg/m ²) (X±SD) | 28,17 ± 4,97 | | 27,14 ± 5,25 | |
| Diastolic blood pressure (mm Hg) (X±SD) | 83,01 ± 11,64 | | 79,89 ± 9,89 | |
| | n | % | n | % |
| Gender: Female | 81 | 85,3 | 74 | 82,2 |
| Male | 14 | 14,7 | 16 | 17,8 |
| Risk factors: | | | | |
| Coronary heart disease* | 86 | 90,5 | 80 | 88,9 |
| Hypertension | 76 | 80,0 | 71 | 78,9 |
| Diabetes mellitus | 25 | 26,3 | 16 | 17,8 |
| Smoking | 18 | 18,9 | 11 | 12,2 |
| Obesity (kg/m ² > 30) | 6 | 6,3 | 8 | 8,9 |
| Cerebrovascular disease** | 8 | 8,4 | 5 | 5,6 |
| Consumption of vasodilators | | | | |
| Nitropental | 58 | 61,1 | 54 | 60,0 |
| Isosorbide mononitrate | 20 | 21,1 | 27 | 30,0 |
| Nitroglycerin | 15 | 15,8 | 5 | 5,6 |
| Other concomitant medications (CM)*** | | | | |
| Antiplatelets | 40 | 42,1 | 40 | 44,4 |
| Calcium antagonists | 30 | 31,6 | 26 | 28,9 |
| Diuretics | 28 | 29,5 | 24 | 26,7 |
| β-blockers | 24 | 25,3 | 26 | 28,9 |
| Oral hypoglycemic drugs | 16 | 16,8 | 6 | 6,7 |
| Digitalics | 13 | 13,7 | 17 | 18,9 |
| Vitamins | 16 | 16,8 | 11 | 12,2 |
| Anxyolytics | 11 | 11,6 | 12 | 13,3 |

n number of patients; X mean, SD standard deviation, *myocardial infarction, unstable angina, coronary surgery, **stroke, ischemic transient attacks; ***CM consumed by >10 study patients, All comparisons were not significant

Table 2: Withdrawal analysis of study patients taking vasodilators

| Withdrawals due to adverse events (AE) | Placebo (n = 95) | | Policosanol (n = 90) | | Total (n = 185) | |
|--|------------------|-------------|----------------------|-------------|-----------------|---------------------------|
| | n | % | n | % | n | % |
| Withdrawals due to vascular serious AE | 15 | 15,8 | 3 | 3,3 | 18 | 9,7 ⁺⁺ |
| Withdrawals due to non-vascular serious AE | 7 | 7,4 | 0 | 0,0 | 7 | 3,8 ⁺⁺ |
| Subtotal due to serious AE | 22 | 23,2 | 3 | 3,3 | 25 | 13,5⁺⁺⁺ |
| Withdrawals due to mild and moderate AE | 1 | 1,1 | 0 | 0,0 | 1 | 0,5 |
| Subtotal due to AE | 23 | 24,2 | 3 | 3,3 | 26 | 14,1⁺⁺⁺ |
| Withdrawals due to other reasons | | | | | | |
| Unsatisfactory efficacy | 4 | 4,2 | 1 | 1,1 | 5 | 2,7 |
| Travels abroad + address changes | 1 | 1,1 | 2 | 2,2 | 3 | 1,6 |
| Unwillingness to follow-up | 1 | 1,1 | 5 | 5,5 | 6 | 3,2 |
| Protocol violations | 2 | 2,1 | 2 | 2,2 | 4 | 2,2 |
| Subtotal due to other reasons | 8 | 8,4 | 10 | 11,1 | 18 | 9,7 |
| Total of withdrawals | 31 | 32,6 | 13 | 14,4 | 44 | 23,8⁺⁺ |

⁺⁺p < 0,01; ⁺⁺⁺p < 0,001 Comparison with placebo (χ² test)

Table 3: Long-term effects of policosanol on lipid profile (X±SD) of study patients

| Treatment | Baseline | 1 year | 2 years | 3 years |
|-------------------------------|--------------------------|----------------------------|----------------------------|----------------------------|
| TC (mmol/L) | | | | |
| Policosanol | 6,80 ± 0,96 | 5,72 ± 0,77 ⁺⁺⁺ | 5,38 ± 0,57 ⁺⁺⁺ | 5,10 ± 0,27 ⁺⁺⁺ |
| Placebo | 6,69 ± 0,80 | 6,58 ± 0,79 | 6,72 ± 0,85 | 6,52 ± 0,85 |
| LDL-C (mmol/L) | | | | |
| Policosanol | 4,83 ± 0,86 | 3,82 ± 0,68 ⁺⁺⁺ | 3,42 ± 0,61 ⁺⁺⁺ | 3,01 ± 0,31 ⁺⁺⁺ |
| Placebo | 4,59 ± 0,84 | 4,61 ± 0,85 | 4,81 ± 0,81 | 4,61 ± 0,84 |
| HDL-C (mmol/L) | | | | |
| Policosanol | 1,16 ± 0,32 ⁺ | 1,20 ± 0,17 | 1,31 ± 0,23 ⁺⁺ | 1,42 ± 0,21 ⁺⁺⁺ |
| Placebo | 1,26 ± 0,32 | 1,16 ± 0,24 | 1,15 ± 0,28 | 1,13 ± 0,20 |
| Triglycerides (mmol/L) | | | | |
| Policosanol | 2,18 ± 0,79 | 1,76 ± 0,50 ⁺⁺⁺ | 1,79 ± 0,30 ⁺⁺⁺ | 1,72 ± 0,19 ⁺⁺⁺ |
| Placebo | 2,36 ± 1,08 | 2,21 ± 0,75 | 2,11 ± 0,59 | 2,11 ± 0,52 |

X mean, SD standard deviation, ⁺p < 0,05; ⁺⁺p < 0,01; ⁺⁺⁺p < 0,0001; ⁺⁺⁺⁺p < 0,00001 ANOVA

Table 4: Long-term effects of policosanol on safety indicators (X±SD) on study patients

| Treatment | Baseline | 1 year | 2 years | 3 years |
|--|---------------|----------------------------|----------------------------|-----------------------------|
| Weight (kg) | | | | |
| Policosanol | 64,45 ± 11,78 | 64,77 ± 10,72 | 64,17- ± 10,25 | 65,16 ± 10,60 |
| Placebo | 66,28 ± 12,95 | 64,84 ± 12,24 | 65,93 ± 12,08 | 66,32 ± 11,15 |
| Pulse (beats/min) | | | | |
| Policosanol | 72,68 ± 7,32 | 72,70 ± 5,95 | 71,12 ± 5,26 | 71,82 ± 3,13 |
| Placebo | 72,33 ± 7,15 | 72,00 ± 5,90 | 72,28 ± 5,10 ⁺ | 72,39 ± 5,24 |
| Diastolic pressure (mm Hg) | | | | |
| Policosanol | 79,89 ± 9,89 | 81,46 ± 5,73 | 79,49 ± 5,79 | 80,22 ± 3,98 |
| Placebo | 83,01 ± 11,64 | 81,60 ± 7,05 | 81,59 ± 7,20 | 81,91 ± 6,47 |
| Systolic pressure (mm Hg) | | | | |
| Policosanol | 133,8 ± 15,03 | 132,7 ± 13,84 | 29,4 ± 15,06 ⁺ | 127,1 ± 10,14 ⁺⁺ |
| Placebo | 137,2 ± 18,14 | 136,2 ± 15,12 | 134,9 ± 12,90 | 134,0 ± 12,80 |
| Alanin amino transferase (U/L) | | | | |
| Policosanol | 18,67 ± 10,10 | 17,77 ± 5,82 ⁺⁺ | 18,22 ± 5,53 ⁺⁺ | 18,44 ± 4,15 ⁺ |
| Placebo | 20,16 ± 10,62 | 21,65 ± 8,18 | 21,69 ± 8,29 | 20,90 ± 4,97 |
| Aspartate amino transferase (U/L) | | | | |
| Policosanol | 21,87 ± 6,78 | 17,69 ± 4,95 ⁺⁺ | 18,71 ± 5,46 ⁺⁺ | 17,37 ± 4,16 ⁺⁺ |
| Placebo | 21,74 ± 9,15 | 20,75 ± 7,19 | 22,24 ± 6,74 | 20,49 ± 5,05 |
| Creatinine (µmol/L) | | | | |
| Policosanol | 91,57 ± 19,41 | 88,78 ± 11,99 | 90,72 ± 10,76 | 91,37 ± 10,71 |
| Placebo | 90,82 ± 17,73 | 90,15 ± 17,67 | 90,35 ± 8,87 | 91,27 ± 9,03 |
| Glucose (mmol/L) | | | | |
| Policosanol | 5,29 ± 0,92 | 5,36 ± 0,78 | 5,20 ± 0,60 | 5,41 ± 0,68 |
| Placebo | 5,50 ± 1,17 | 5,54 ± 1,04 | 5,30 ± 0,63 | 5,29 ± 0,60 |

X mean, SD standard deviation, ⁺p < 0,05; ⁺⁺p < 0,01 ANOVA

Table 5: Serious adverse events (SAE) in study patients taking vasodilators

| Endpoints | Placebo (n= 95) | | Policosanol (n = 90) | |
|------------------------------------|-----------------|-------------|----------------------|--------------------------|
| | n | % | n | % |
| All cardiovascular SAE | 13 | 13,7 | 2 | 2,2 ⁺⁺ |
| All cerebrovascular SAE | 2 | 2,1 | 1 | 1,1 |
| All vascular SAE | 15 | 15,8 | 3 | 3,3⁺⁺ |
| Non-vascular SAE | 7 | 7,4 | 0 | 0,0 ⁺⁺ |
| All SAE (fatal + non fatal) | 22 | 23,2 | 3 | 3,3⁺⁺⁺ |
| Fatal SAE (Deaths) | | | | |
| Cardiovascular | 5 | 5,3 | 0 | 0,0 ⁺ |
| Cerebrovascular | 1 | 1,1 | 0 | 0,0 |
| Deaths due to vascular SAE | 6 | 6,3 | 0 | 0,0⁺ |
| Non-vascular deaths | 0 | 0,0 | 1 | 1,1 |
| All mortality | 6 | 6,3 | 1 | 1,1 |

Study subjects are counted only once with a specific endpoint; However, they may be listed more than once because of experiencing an event included in more than one endpoint analysis, ⁺p < 0,05; ⁺⁺p < 0,01; ⁺⁺⁺p < 0,001 Comparison with placebo (χ² test)

Table 6: Moderate and mild adverse events (AE) reported by patients

| Moderate AE | | | | |
|--|------------------|-------------|--------------------|--------------------------|
| Body System/AE | Placebo (n = 95) | | Policosanol (n=90) | |
| Muscle-skeletal system disorders | | | | |
| Bursitis | 0 | 0,0 | 1 | 1,1 |
| Fractures | 1 | 1,0 | 0 | 0,0 |
| Cardiovascular disorders | | | | |
| Dyspnea at effort | 1 | 1,0 | 0 | 0,0 |
| Moderately uncontrolled hypertension | 0 | 0,0 | 1 | 1,1 |
| Respiratory system disorders | | | | |
| Asthma | 2 | 2,1 | 0 | 0,0 |
| Pneumonia | 2 | 2,1 | 1 | 1,1 |
| Reproductive disorders | | | | |
| Breast dysplasia | 0 | 0,0 | 1 | 1,1 |
| White cell and RES disorders | | | | |
| Lymphangitis | 1 | 1,0 | 0 | 0,0 |
| Urinary system disorders | | | | |
| Renal sepsis | 3 | 3,2 | 0 | 0,0 |
| Mild AE | | | | |
| Skin and appendages disorders | | | | |
| Mouth dryness | 2 | 2,1 | 0 | 0,0 |
| Muscle-skeletal system disorders | | | | |
| Arthralgia | 3 | 3,2 | 2 | 2,2 |
| Legs pain | 2 | 2,1 | 0 | 0,0 |
| Muscle cramps | 4 | 4,2 | 0 | 0,0 ⁺ |
| Central and peripheral nervous system disorders | | | | |
| Dizziness | 1 | 1,0 | 1 | 1,1 |
| Headache | 1 | 1,0 | 0 | 0,0 |
| Gastrointestinal system disorders | | | | |
| Diarrhoea | 4 | 4,2 | 0 | 0,0 ⁺ |
| Vomiting | 1 | 1,0 | 0 | 0,0 |
| Endocrine disorders | | | | |
| Hypoglycemia | 0 | 0,0 | 1 | 1,1 |
| Cardiovascular disorders | | | | |
| Chest pain | 9 | 9,5 | 1 | 1,1 ⁺ |
| Mildly uncontrolled hypertension | 0 | 0,0 | 1 | 1,1 |
| Heart rate and rhythm disorders | | | | |
| Tachycardia | 0 | 0,0 | 1 | 1,1 |
| Respiratory system disorders | | | | |
| Pneumonia | 1 | 1,0 | 0 | 0,0 |
| Urinary system disorders | | | | |
| Renal colic | 0 | 0,0 | 1 | 1,1 |
| Renal sepsis | 1 | 1,0 | 0 | 0,0 |
| Body as a whole | | | | |
| Anorexia | 1 | 1,0 | 0 | 0,0 |
| Asthenia | 0 | 0,0 | 2 | 2,2 |
| Fever | 1 | 1,0 | 0 | 0,0 |
| Loss on weight | 1 | 1,0 | 1 | 1,1 |
| Patients with moderate or mild AE | 28 | 29,5 | 10 | 11,1⁺⁺ |

⁺p < 0,05; ⁺⁺p < 0,01 Comparison with placebo (χ^2 test)

At randomisation both groups were similar. Hence, random allocation to treatment was adequate and groups were homogeneous. The large proportion of women is characteristic of the patients attending to the Policlinics of this area,³⁸ and also reflects the high motivation of such women to participate and adhere to study protocol.

The preponderance of the use of nitropental as compared with other vasodilators was consistent with the situation present in Cuban routine clinical practice in the time of the trial. Consumption of other concomitant drugs was high, a common finding in the elderly. Thus, the present report is not conducted in an ideal population only consuming vasodilators and placebo or policosanol, but also receiving other concomitant therapies, as occurs with real patients in clinical practice. The other concomitant drugs consumed by study patients were consistent with their risk condition.

As expected, policosanol showed persistent efficacy for lowering LDL-C, the primary efficacy variable, CT, whereas increased

HDL-C.¹⁰⁻²³ Reductions on TG were greater than in previous studies, a finding without conclusive explanation.

The frequency of withdrawals in placebo was greater than in policosanol group, a finding related with discontinuations due to AE, since the frequency of withdrawals due AE, mostly SAE, was greater in placebo than in policosanol group, while the frequency of other withdrawals was similar.

The lesser extent of SAE in policosanol respect to placebo is consistent with drug effects, since most SAE were of vascular nature and policosanol lowers LDL-C and also inhibit platelet aggregation and LDL oxidation, all consistent with vascular protection.

Policosanol was safe and well tolerated. No policosanol-related impairment of safety indicators was observed. Thus, the additional reduction of systolic pressure (and in lesser extent of diastolic pressure) induced by policosanol was not considered as a drug-related AE, since individual values remained within normal range and hypotension was not referred as AE. By the

contrary, in a population with a high frequency of CHD and hypertension, like the study population, such effect could be beneficial to reduce the global atherosclerotic risk of the patients, mainly because a decrease on systolic pressure has been associated to a reduction of coronary events in the elderly.³⁹

On the other hand, the reduction of serum transaminases here reported agrees with previous results, underlying that policosanol does not affect liver function. Although the conclusive explanation of the policosanol-induced reduction of transaminase values is not available, recent experiences suggest that policosanol can exert some protective effects on liver cells.⁴⁰

AE reports did not show increases resulting from concomitant use of policosanol and vasodilators. Conversely, the frequency of both SAE and other AE (mild + moderate) was lower in policosanol than in placebo. This result, together with withdrawal analysis, indicates that concomitant administration of policosanol and vasodilators is well tolerated and potential risk due to adverse DDI is low.

CONCLUSION

Policosanol was well tolerated in older patients taking vasodilators, not affecting safety indicators or increasing AE compared with placebo. Other benefits were observed in policosanol group, such as the additional reduction of systolic pressure and a lesser extent of SAE, in addition to the expected cholesterol-lowering efficacy of policosanol. These results show that policosanol long-term consumed by older individuals taking vasodilators did not induce adverse DDI.

REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report from the American Heart Association. *Circulation* 2016; 133:e38-e360.
2. Aronow WS, Frishman WH. Management of hypercholesterolemia in older persons for the prevention of cardiovascular disease. *Cardiol Rev* 2010; 18:132-140.
3. Cohen JD, Cziraky MJ, Cai Q, et al. 30-year trends in serum lipids among United States adults: results from the National Health and Nutrition Examination Surveys II, III, and 1999-2006. *Am J Cardiol* 2010; 106:969-975.
4. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract* 2012; 18(1):1-78.
5. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014; 64:485-494.
6. Cholesterol Treatment Trialists' (CTT) Collaboration, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomized trials. *Lancet* 2015; 385:1397-1405.
7. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. on behalf of the PROSPER Study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled study. *Lancet* 2002; 360:1623-1630.
8. Expert Panel of Detection, Evaluation and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Final report. *Circulation* 2002; 106:3143-3181.
9. Félix FJ, Grau M, Fernández D. Cholesterol and Cardiovascular Disease in the Elderly. *Facts and Gaps. Aging Dis* 2013; 4(3):154-169.
10. Mas R. Policosanol Drugs of the Future 2000; 25:569-586.
11. Benítez M, Romero C, Más R, Fernández L, Fernández JC. A comparative study of policosanol versus pravastatin in patients with type II hypercholesterolemia. *Curr Ther Res* 1997; 58:859-867.
12. Canetti M, Morera M, Más R, Illnait J, Fernández L, Fernández JC, et al. A two years study on the efficacy and tolerability of policosanol in patients with type II hyperlipoproteinaemia. *Int J Clin Pharmacol Res* 1995; XV:159-165.
13. Más R, Castaño G, Illnait J, Fernández L, Fernández JC, Alemán C, et al. Effects of policosanol in patients with type II hypercholesterolemia and additional coronary risk factors. *Clin Pharmacol Ther* 1999; 65(4):439-447.
14. Castaño G, Canetti M, Moreira M, Tula L, Más R, Illnait J, et al. Efficacy and tolerability of policosanol in elderly patients with type II hypercholesterolemia: A 12 months study. *Curr Ther Res* 1995; 56(8):819-828.
15. Ortensi G, Gladstein H, Valli H, Tesone PA. A comparative study of policosanol versus simvastatin in elderly patients with hypercholesterolemia. *Curr Ther Res* 1997; 58:390-401.
16. Castaño G, Más R, Arruzazabala ML, Noa M, Illnait J, Fernández JC, et al. Effects of policosanol and pravastatin on lipid profile, platelet aggregation and endothelium in older hypercholesterolemic patients. *Int J Clin Pharm Res* 1999; 19:105-116.
17. Castaño G, Más R, Fernández JC, Illnait J, Fernández L, Alvarez E. Effects of policosanol in older patients with type II hypercholesterolemia and high coronary risk. *J. Gerontol Sci Med Sci* 2001; 56(3):186-192.
18. Fernández JC, Más R, Castaño G, Menéndez R, Amor AM, González RM, Alvarez E. Comparison of the efficacy, safety and tolerability of policosanol versus fluvastatin in elderly hypercholesterolemic women. *Clin Drug Invest* 2001; 21(2):103-113.
19. Más R, Castaño G, Fernández L, Illnait J, Fernández J, Alvarez E. Effects of policosanol on lipid profile and cardiac events in older hypercholesterolemic patients with coronary disease. *Clin Drug Invest* 2001; 21(1):485-497.
20. Castaño G, Más R, Fernández J, Fernández L, Illnait J, López E. Effects of policosanol on older patients with hypertension and type II hypercholesterolemia. *Drugs R&D* 2002; 3(3):159-172.
21. Castaño G, Mas R, Fernández L, Illnait J, Mesa M, Alvarez E, Lezcay M. Comparison of the efficacy, safety and tolerability of policosanol versus atorvastatin in elderly patients with Type II hypercholesterolemia. *Drugs & Aging* 2003; 20:153-163.
22. Torres O, Agramonte AJ, Illnait J, Más R, Fernández L, Fernández JC. Treatment of hypercholesterolemia in NIDDM with policosanol. *Diabetes Care* 1995; 18(3):393-397.
23. Crespo N, Alvarez R, Más R, Illnait J, Fernández L, Fernández JC. Effect of policosanol on patients with non-insulin-dependent diabetes mellitus (NIDDM) and hypercholesterolemia. A pilot study. *Curr Ther Res* 1997; 58(1):44-51.
24. Castaño G, Menéndez R, Más R Amor A, Fernández JC, González RM, et al. Effects of policosanol and lovastatin on lipid profile and lipid peroxidation in patients with dyslipidemia associated with type 2 diabetes mellitus. *Int J Clin Pharmacol Res* 2002; 22(3-4):89-99.
25. Menéndez R, Fernández I, Del Río A, González RM, Fraga V, Amor AM, Más R. Policosanol inhibits cholesterol biosynthesis and enhances LDL processing in cultured human fibroblasts. *Biol Res* 1994; 27:199-203.
26. Menéndez R, Arruzazabala ML, Más R, del Río A, Amor AM, González RM, et al. Cholesterol-lowering effect of

- policosanol on rabbits with hypercholesterolemia induced by a wheat starch-casein diet. *Brit J Nutr* 1996; 77:923-932.
27. Menéndez R, Amor A, Rodeiro I, González RM, Acosta P, Alfonso J, Más R. Policosanol modulates HMGCoA reductase activity in cultured fibroblasts. *Arch Med Res* 2001; 32:8-12.
 28. Arruzazabala ML, Valdés S, Más R, Fernández L, Carbajal D. Effect of policosanol successive dose increases on platelet aggregation in healthy volunteers. *Pharmacol Res* 1996; 34:181-185.
 29. Menéndez R, Más R, Amor AM, González RM, Fernández JC, Rodeiro I, et al. Effects of policosanol treatment on the susceptibility of low density lipoprotein (LDL) isolated from healthy volunteers to oxidative modification in vitro. *Brit J Clin Pharmacol* 2000; 50:255-262.
 30. Menéndez R, Más R, Amor AM, Fernández JC, González RM. Effects of policosanol on the susceptibility of low-density lipoprotein (LDL) isolated from on hypercholesterolemic patients at high coronary risk to in vitro copper-mediated lipid peroxidation. A Randomised, Double-Blinded Pilot Study. *Curr Ther Res* 2000; 61(9):609-620.
 31. Fernández L, Más R, Illnait J, Fernández JC. Policosanol: results of a postmarketing surveillance control on 27 879 cases. *Curr Ther Res* 1998; 59:717-722.
 32. Más R, Rivas P, Izquierdo JE, Hernández R, Fernández L, Fernández JC, et al. Pharmacoeconomic study of policosanol. *Curr Ther Res* 1999; 60(8):458-467.
 33. Rodeiro I, Alemán CL, Más R, Acosta PC, Rodríguez MD, Gamez R, et al. Efectos del policosanol sobre las enzimas microsomas hepáticas en ratas Sprague Dawley. *Rev CENIC Cien Biol* 2001; 31(2):113-116.
 34. Aronow WS, Fleg JL, Pepine CJ, for the ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents developed in collaboration with the American Academy of Neurology, American Geriatrics Society, American Society for Preventive Cardiology, American Society of Hypertension, American Society of Nephrology, Association of Black Cardiologists, and European Society of Hypertension. *J Am Soc Hypertens* 2011; 5(4):259-352.
 35. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. *J Hypertens* 2016; 34(10):1921-1932.
 36. Mas R, Castaño G, Fernández J, Fernández L, Illnait J. Effects of policosanol on morbidity and mortality in older hypercholesterolemic patients. *J Am Coll Cardiol* 2002; 39 (Suppl B):429B.
 37. Schectman G, Hiatt J. Drug therapy for hypercholesterolemia in patients with cardiovascular disease: factors limiting achievement of lipid goals. *Am J Med* 1996; 100:197-204.
 38. Cuban National Statistics Bureau of the Ministry of Public Health. Annual Health Statistics Report. Havana: Ministry of Public Health, 2015.
 39. Denker MG, Cohen DL. What is an appropriate blood pressure goal for the elderly: review of recent studies and practical recommendations. *Clin Interv Aging* 2013; 8:1505-1517.
 40. Noa M, Mendoza S, Más R, Mendoza N. Effect of policosanol on tetrachloride-induced acute liver damage in Sprague Dawley rats. *Drugs in Development* 2003; 4(1):29-35.

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